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SYNTHESIS AND RECEPTOR AFFINITY OF POLYSUBSTITUTED ADENOSINES

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ABSTRACT: In a search for potent and selective adenosine agonists it has been found that 2-hexynyladenosine-5'-N-ethyluronamide (HENECA) displays high affinity at rat A_{2A} receptor combined with a good A_{2A} vs A₁ selectivity. The finding that HENECA shows good affinity also for A₃ receptors prompted us to investigate the effect of various substituents in different positions of this molecule.

INTRODUCTION

Investigating new and selective adenosine receptor ligands it has been found that 2-hexynyladenosine (HEAdo, **1**) is endowed with high affinity for adenosine receptor.¹ The introduction of an ethylcarboxamido group at the 5'-position led to 2-hexynyladenosine-5'-N-ethyluronamide (HENECA, **2**) which displays high affinity at rat A_{2A} receptor combined with a good A_{2A} vs A₁ selectivity.² HENECA was also found to possess good affinity for A₃ receptor subtypes.³ Furthermore, NECA analogues containing N⁶ arylcarbamoyl groups have shown high affinity at rat A₁ and A₃ adenosine receptors.⁴

These findings prompted us to investigate the effect of different substituents in N⁶- and 5'-positions of HEAdo.

The synthesis of the new compounds will be published elsewhere.

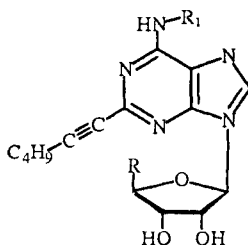
RECEPTOR AFFINITY

All the synthesized compounds were evaluated at the human recombinant adenosine receptors, stably transfected into Chinese hamster ovary (CHO) cells, utilizing radioligand binding studies (A₁, A_{2A}, A₃) or adenyl cyclase activity assays (A_{2B}) (Table 1).⁵

Preliminary results showed that the 2-hexynyl adenosine (**1**) showed high affinity for A₁, A_{2A}, and A₃ receptor, while the affinity for the A_{2B} subtype was very low (EC₅₀ > 100 μM). The substitution of the hydroxymethyl group in the 5'-position with an ethylcar-

boxamido led to a compound (HENECA, **2**) with comparable affinity at A_1 and increased affinity at A_{2A} , A_{2B} , and A_3 receptors. Replacement of the ethyl group of the carboxamide by a cyclopentyl ring (**3**), as well as substituents in the N^6 position (**4**, **5**, **6**), brought about a decrease of the affinity at all the receptor subtypes. These data demonstrate the negative interdependence, in terms of affinity, of these substituents at C^2 - and N^6 -positions of the purine moiety.

Table 1. Affinities of selected adenosine derivatives in radioligand binding assays at human A_1 , A_{2A} and A_3 , and in adenylyl cyclase assays at human A_{2B} adenosine receptors.



Cpd	R	R ₁	K _i or EC ₅₀ (nM)			
			K _i (A_1)	K _i (A_{2A}) ^a	EC ₅₀ (A_{2B}) ^b	K _i (A_3) ^c
1	HOCH ₂	H	45 ^d	11	>100,000	7.7
2	EtNHCO	H	60 ^d	6.4	6,100	2.4
3	cC ₅ H ₉ NHCO	H	403 ^d	49	>100,000	16
4	EtNHCO	cC ₅ H ₉	73 ^d	178	>100,000	65
5	EtNHCO	3-Cl-Ph-NH-CO	2,000 ^e	>10000	>100,000	36
6	EtNHCO	4-CH ₃ O-Ph-NH-CO	428 ^e	>10000	>100,000	57

^aDisplacement of specific [³H]NECA binding in CHO cells, stably transfected with human recombinant A_{2A} adenosine receptor, expressed as K_i (nM). ^bMeasurement of receptor-stimulated adenylyl cyclase activity in CHO cells, stably transfected with human recombinant A_{2B} adenosine receptor, expressed as EC₅₀ (nM). ^cDisplacement of specific [³H]NECA binding in CHO cells, stably transfected with human recombinant A_3 adenosine receptor, expressed as K_i (nM). ^dDisplacement of specific [³H]DCPX binding in CHO cells, stably transfected with human recombinant A_1 adenosine receptor, expressed as K_i (nM). ^eDisplacement of specific [³H]PIA binding in rat brain membranes (A_1) expressed as K_i (nM).

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